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# Endocrine Disorders as a Contributory Factor to Neoplasia in SJL/J Mice[1,2]

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**SUMMARY—We studied the endocrine status of SJL/J mice. Light and electron microscopy revealed that the adenohypophyses of both sexes became progressively infiltrated with an abnormal number of gonadotropin-producing cells that probably secreted large amounts of luteotropic hormone. The ovaries had numerous large corpora lutea even in animals over 1 year of age with reticulum cell neoplasms. The adrenal cortexes of female mice showed no regression of the reticular zone. In accordance with the anomalous condition of the adenohypophysis and ovary, females had abnormal estrous cycles, with prolonged diestrus and consequent reduction in fertility. These data were discussed in the context of hormone environment versus onset of systemic neoplastic disease and the relationship between hormone dependence and leukemic virus expression.—J Natl Cancer Inst 53: 731–744, 1974.**

SJL/J MICE, which develop a high incidence of spontaneous reticulum cell sarcomas or neoplasms at an early age, have been investigated intensively by oncologists. This reticulum cell neoplasm, defined as type B (RCNB) by Dunn (*1*), kills virtually all SJL/J mice of both sexes between 8 and 14 months of age (mean survival time: 13.3 months). Since it resembles Hodgkin's disease in humans, it is sometimes called Hodgkin's-like disease of mice. Descriptions of this disease in SJL/J and other strains of mice have been detailed in (*1–7*). Study of this neoplastic process in the SJL/J strain is especially compelling, inasmuch as reticulum cell neoplasms, contrary to lymphoma and lymphosarcoma, are generally rare in young mice and found only sporadically in old animals (*8*).

One of the most prominent aspects of the disease in SJL/J mice is the early diffuse or focal proliferation of modified reticulum cells, histiocytes, plasma cells, and lymphocytes, mostly in the lymph nodes but also in other lymphoid organs such as spleen and thymus. At an early age, these mice show hyperplasia of the thymus and peripheral lymphatic tissues (*9*). Their immune status in relation to age and development of reticulum cell neoplasms has been explored by Haran-Ghera et al. (*10*).

Arnesen (*11*) showed that AKR mice, which develop spontaneous leukemia, have morphologic abnormalities in the adrenals. Also, Levine and Treiman (*12*) found that the plasma corticosterone response to stress in AKR mice is significantly lower than in other strains.

Since proliferation and differentiation of lymphoid and hematopoietic cells largely depend on the hormone environment, a reasonable assumption was that a primary hormone derangement could be responsible for the early and progressive alterations of lymphatic tissues in SJL/J mice. Moreover, a specific chronic endocrine stimulus could be responsible for the changes observed concomitantly with viral agents or could possibly alone induce the onset of RCNB. Therefore, studies designed to test the validity of this assumption were based largely on determining the endocrine status of SJL/J mice of different ages and sex.

## MATERIALS AND METHODS

*Animals.*—Inbred SJL/J and C57BL/6 mice, cesarean-originated and barrier-sustained, were raised and maintained in the Animal Breeding Center, The Weizmann Institute of Science.

*Histology.*—Groups of 3–4 females and in some cases, males, 1 day to 12 months of age were killed. The tissues were fixed in Bouin's fluid and embedded in paraffin, and the sections were stained with hematoxylin-eosin-phosphomolybdic acid-light green. Sections of the following tissues were prepared and examined: brain; hypophysis; heart; thoracic aorta; thymus; axillary, mesenteric and inguinal lymph nodes; liver; spleen; thyroid; pancreas; kidneys; adrenals; testes; and ovaries. Histologic examination was repeated in groups in which abnormalities were found. Because of difficulties in identification of different cell types in the adenohypophysis by light microscopy, sections of the adenohypophyses of the mice were also analyzed by electron microscopy.

Light micrographs of sagittal sections of the adrenal glands at the vena centralis level of the medulla were taken to evaluate possible structural differences. Our criterion for judging the size of the zona fasciculata was not based on overall magnification of the gland but rather on the ratio between the size of the cortical zones and the size of the medulla.

*Electron microscopy.*—The adenohypophyses of 2- and 5-month-old male and female SJL/J and C57BL/6 mice (4 in each group) were fixed in glutaraldehyde-osmium, embedded, sectioned, and examined as previously described by Bianchi et al. (*13*). Identically oriented and located ultrathin sections of the latero-distal part of the adenohypophysis were selected by light microscopy and used to compare and identify cell types by electron microscopy.

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*Hormone determinations.*—Pooled sera of groups of 5–10 mice of both strains were obtained by rapid collection of blood from the retro-orbital plexus under light ether anesthesia. The animals were always bled in the late morning (10:00–11:00 a.m.) and under the same conditions to minimize stress and the daily physiologic variations of hormone levels in blood. Serum or plasma was kept frozen at −20° C until measurements were made. Corticosterone was measured by a double isotope dilution derivative assay (*14, 15*). Determinations of hormones were repeated 3–4 times in animals of same age and sex.

*Test for hypophyseal and adrenal function.*—To evaluate hypophyseal function for adrenocorticotropic hormone (ACTH) secretion under stress or production of corticosterone under exogenous ACTH treatment, we stressed groups of 2-, 4-, and 6-month-old female SJL/J mice (10 mice per group) by keeping them for 30 minutes at +5° C and pinching the tails with pincettes, or by giving them intraperitoneal (ip) injections of 10 μg ACTH (Synacthen; Ciba-Geigy, Basel, Switzerland) in 0.5 ml saline. Controls were either untouched or given injections of 0.5 ml saline. Immediately after the stressing procedure or 1 hour after the ACTH injection, the mice were bled. The stressing procedure increased the release of endogenous ACTH in the adenohypophysis and indicated whether the cortex of the adrenal gland responded normally with augmented production of corticosterone. Inoculation of ACTH revealed whether the adrenal cortex responded with increased output of corticosterone to stimulation with excess exogenous ACTH.

*Estrous cycle.*—Daily vaginal smears were taken from female SJL/J mice 2 and 5 months of age, and the pattern of the estrous cycle was evaluated.

*Operative procedures.*—For histologic evaluation of the possible direct effect of thymus and ovaries on the structure of the adrenals and of the thymus on the structure of the ovaries (*16,17*), groups of 10–12 newborn SJL/J mice were thymectomized by suction within 12 hours after delivery. Controls were sham operated. They were all killed at 30 days of age and the tissues examined histologically. Other groups of female SJL/J mice (10 animals in each group) were thymectomized or ovariectomized at 30 days of age. Another group of the same age was thymectomized *and* ovariectomized. The mice were killed 15 or 30 days after the operations and the tissues examined histologically.

## RESULTS

### Light Microscopy Findings

The histopathology of all lymphatic organs of SJL/J mice before and during development of the disease was described in (*1–10*); we found further alterations and pathologic changes in the adenohypophysis, adrenal cortex, ovaries, and small vessels.

*Adenohypophysis.*—The anterior pituitary glands of SJL/J mice of both sexes had a greater number of chromophobic or slightly acidophilic cells than did C57BL/6 mice of the same age and sex. This cell type was clearly identified by electron microscopy (*see* below). The number increased steadily with age, and clusters of cells formed especially in the laterodistal portion of the anterior pituitary gland normally occupied by somatotropin-producing (STH) acidophilic cells in C57BL/6 and other strains of mice. Although present, STH cells in SJL/J mice were fewer than in other strains.

*Adrenals.*—The adrenal cortexes of SJL/J mice had a remarkably smaller zona fasciculata and an abnormally enlarged zona reticularis occupying most of the cortex (figs. 1, 2). What we call "zona reticularis" corresponds to the much discussed transitory or x-zone of the adrenal cortex of mice (*18–22*). We use this terminology only for the topographic description of the histologic findings. This zona reticularis, which normally in other strains of mice can be seen until puberty in males and until the first pregnancy in females, disappeared also in male SJL/J mice at puberty; it was maintained in virgin SJL/J females for a long time and could be seen even at the age of 6–8 months (figs. 3–5), whether reticulum cell sarcomas were already present or not.

The overall picture indicated a hypofunction of the zona fasciculata, which is under hypophyseal control through ACTH. This zone is responsible for secretion of glucocorticosteroids such as corticosterone. The width of the zona fasciculata decreased even further with age in SJL/J mice and was reduced to a narrow strip in 8- to 12-month-old animals (figs. 6, 7). Absence of the thymus in athymic nude mice has been recently shown to influence the size and duration of the zona fasciculata (*16*). However, neither neonatal thymectomy, gonadectomy, nor removal of both thymus and gonads at 30 days of age seemed to affect the formation, size, and duration of the zona reticularis or the size of the zona fasciculata in SJL/J mice. This agrees with the suggestion that this reticular zone (or x-zone) in mouse adrenal cortex is directly controlled by gonadotropins (*22*).

Numerous large foci of extramedullary hematopoiesis were observed in the adrenal cortexes of SJL/J mice until they were 10 days of age.

*Ovaries.*—The fertility of SJL/J females (expressed as average number of litters per female) was much more reduced than in other strains (4.5–9 litters; A. Meshorer, personal communication). The ovaries of SJL/J mice maintained large numerous corpora lutea (figs. 8, 9). These abnormally large corpora lutea were visible until 7–8 months of age, when ovulation apparently ceased (fig. 10); sometimes they were still present in animals 1 year of age, with diffuse or localized RCNB (figs. 11, 12). The fallopian tubes and the other components of the ovaries of 7- to 8-month-old SJL/J mice appeared sclerotic. Neonatal or adult thymectomy did not affect formation, development, number, or size of corpora lutea in the ovaries of these mice.

*Vessels.*—Diffuse vasculitis was confined to the small arterioles in almost all organs. The aorta did not seem to be involved. The alteration, thickening, and damage of the small arteries was remarkable. In view of the endocrine alterations in SJL/J mice, the pathogenesis is being investigated.

### Hormone Levels

Thyroxine levels in SJL/J mice were normal, as compared to C57BL/6 mice. By contrast, levels of corticosterone in the blood of SJL/J mice were a half to a third those in C57BL/6 mice of the same age and sex (table 1). The stress test as well as injection of ACTH induced approximately threefold increases in this parameter. The level of testosterone was normal or below normal in young male SJL/J mice, whereas it reached high levels in 6-month-old mice (table 1).

### Estrous Cycle

Most female SJL/J mice had a remarkably prolonged diestrus, and therefore the whole cycle was lengthened (8–9 days instead of 4–5 days).

### Electron Microscopy

As confirmed by light microscopy, indirectly by the presence of gigantic long-lasting corpora lutea in the ovaries, and by the prolonged diestrus, the adenohypophyses of male and female SJL/J mice showed massive infiltration with luteotropic cells [ε-cells, according to the classification of Barnes (*23*)]. These cells occupied most of the gland, but especially the laterodistal portions, and increased in number with age. They constituted a majority and infiltrated all portions of the gland both in males and females. Other cell types were present, though the number of STH cells was greatly reduced in SJL/J mice as compared to C57BL/6 and other strains (*13*, *24*) (figs. 13, 14). Therefore, a massive hyperplasia of luteotropic cells was present in the anterior pituitaries of SJL/J mice. Figures 13 and 14 show selected fields exemplifying the predominance of luteotropic cells in the adenohypophyses of SJL/J mice.

## DISCUSSION

This investigation has shown that, by various criteria, SJL/J mice are endocrinologically abnormal. The cytology of the adenohypophysis deviates from that of other strains of mice in that it contains many gonadotropic cells (luteotropic cells, ε-cells) (*13*), characterized by polymorphic granuli in the Golgi zone (figs. 13, 14). The abnormality is present at 2 months of age and increases progressively with age. At 5 months, most cells of the anterior pituitary gland are luteotropic, but there is a sharp reduction in number of STH cells which, in other strains of mice of the same age and sex, normally constitute the majority in the same portions of the adenohypophysis. In parallel with the anticipated high production of gonadotropins, the ovaries of female SJL/J mice contain numerous large corpora lutea that occupy most of the gland (figs. 8–12). They are maintained even in the atrophic glands of 10–12-month-old mice, in which no oocytes and follicles are left and no ovulation occurs. From these data we infer that production of gonadotropins is abnormally and chronically high in SJL/J mice. As expected, the estrous cycle in adult female SJL/J mice is abnormal and diestrus, which is maintained by luteotropic hormone and progesterone, is prolonged.

A collateral observation, which supports the concept of a pathologic and progressively increasing high input of gonadotropins in SJL/J mice and thus excessive stimulation of testicular function, is that male SJL/J mice cannot be housed in the same cage because their extreme aggressiveness causes continued fighting and death. In fact, the level of testosterone in sera of 2-month-old SJL/J males is comparable to that in C57BL/6 males, but is much higher in 6-month-old mice (table 1). All long-term experiments with SJL/J mice must therefore be done with females.

The adrenal cortexes of SJL/J mice are abnormal. The reticular zone is large and, in virgin females, does not show the normal involution, whereas the zona fasciculata is thin (figs. 1–7). The decreased serum corticosterone level in SJL/J mice may be due to an abnormally low level of corticosterone-binding globulin in these animals. However, the narrow width of the zona fasciculata of the adrenal cortex is more suggestive of a decreased rate of corticosterone production. The normal increase in plasma corticosterone in response to exogenous ACTH excludes a primary adrenocortical lesion, such as a defect in corticosteroid biosynthesis. The normal response to the stress demonstrates that the pituitary gland can still secrete ACTH on demand and is evidence against a primary failure of the ACTH-producing pituitary cells. It seems more likely that a lowered baseline secretion of

TABLE 1.—*Levels of thyroxine, testosterone, and corticosterone in sera of SJL/J and C57BL/6 mice**

| Strain | Age (days) | Sex | Thyroxine | Corticosterone | Corticosterone after ACTH† | Corticosterone after stress | Testosterone |
|---|---|---|---|---|---|---|---|
| SJL/J | 30 | F | 9. 9 | 6. 0 | — | — | — |
| C57BL/6 | 30 | F | 10. 0 | 16. 9 | — | — | — |
| SJL/J | 70 | M | — | — | — | — | 211 |
| C57BL/6 | 70 | M | — | — | — | — | 291 |
| SJL/J | 150 | F | 10. 6 | 8. 1 | — | — | — |
| C57BL/6 | 150 | F | 8. 3 | 20. 3 | — | — | — |
| SJL/J | 160 | F | — | — | — | — | 38 |
| C57BL/6 | 160 | F | — | — | — | — | 102 |
| SJL/J | 180 | F | — | 10. 4 | 27. 0 | 30. 9 | — |
| SJL/J | 180 | M | — | — | — | — | 350 |
| C57BL/6 | 180 | M | — | — | — | — | 155 |

*Values of thyroxine and corticosterone are expressed as μg/100 ml serum; values of testosterone, as ng/100 ml serum.
†The mice were bled 1 hour after ip injection of 10 μg ACTH.

corticosterone might be due to a functional disturbance of the hypothalamus.

Hormones profoundly affect all steps in the ontogenic maturation and proliferation of thymolymphatic and hematopoietic tissues (*24*, *25*). Thus any change in hormone environment will be reflected in variations in the cell dynamics. Cells of the thymolymphatic, hematopoietic, and reticular tissues are highly sensitive targets of hormones during ontogeny. In SJL/J mice, a specific congenital tendency to increased production of gonadotropins probably affects both gonadal and adrenal functions. The consequences of the hormone imbalance in SJL/J mice is most dramatically expressed in the cytology, development, and alteration of the thymolymphatic, reticular, and hematopoietic tissues, though direct proof must still be provided. In SJL/J mice, cells of the thymus, lymph nodes, and bone marrow and reticulum cells are all affected, but certainly the cell type that is involved most and responds with massive proliferation in this SJL/J-specific hormone imbalance is the reticulum cell. An indication of the far-reaching implications of this relationship is that oral treatment of SJL/J mice with dimethylbenzanthracene (DMBA), which destroys oocytes in the ovaries (*26*) and provokes a deep and obvious change in the hormone environment, results in early appearance of lymphosarcoma in the thymus rather than reticulum cell sarcoma in the lymph nodes (*3*).

Hellmann and Fowler (*27*) and Fowler et al. (*28*) found that estrogens activate the expression of antigens of murine C-type virus (which has been identified as the cause of leukemia in mice) and promote synthesis of RNA-directed DNA polymerase. The obligatory role of hormones for replication of tumor virus has also been recognized recently in mammary cancer of mice (*29*, *30*). Therefore, the links to consider now are those between hormones, cell types, viruses, and enzymes. For example, removal of the thymus, a sensitive target for hormones (*31*), prevents appearance of leukemia induced by X-irradiation (*32*) or carcinogens (*33*). Clearly the thymus is, in that specific instance, species, and circumstance, the organ in which the fortuitous combination of this organ, cell, hormone and virus factors are operative. Change in *one* of these conditions—as thymectomy or, as in SJL/J mice, the hormone imbalance—will either prevent or delay onset of leukemia. In this strain thymectomy does *not* prevent onset of DMBA-induced lymphatic leukemia (*3*).

The similarity between type-B reticulum cell sarcoma (Hodgkin's-like disease in mice) and Hodgkin's disease in humans is still doubtful (*34*); however, the hormone conditions in preleukemic and leukemic states and in Hodgkin's disease have been almost completely neglected and warrant some consideration. Certain pre-existent congenital, subpathologic, or paraphysiologic hormone imbalances in families with high incidence of certain neoplasms might affect onset of the tumors.

Whether or not systemic neoplasms in humans can be shown to have a viral causation, clearly viruses need certain hormones to express themselves and their carcinogenic properties. For example, the notion that estrogens "promote" leukemia in mice should now be recast as a possible estrogen-dependent expression or promotion and stimulation of replication of ubiquitous viruses through increased synthesis of RNA-dependent DNA polymerase, which has a high concentration in the thymus. In this situation the quantitative aspect is clear because removal of the thymus, which represents the privileged target for hormones and viruses, effectively prevents the onset of leukemia.

We are now attempting to induce, change, or "modulate" the onset, pattern, and development of leukemias and RCNB in SJL/J and other strains of mice by manipulation of their hormone environment.

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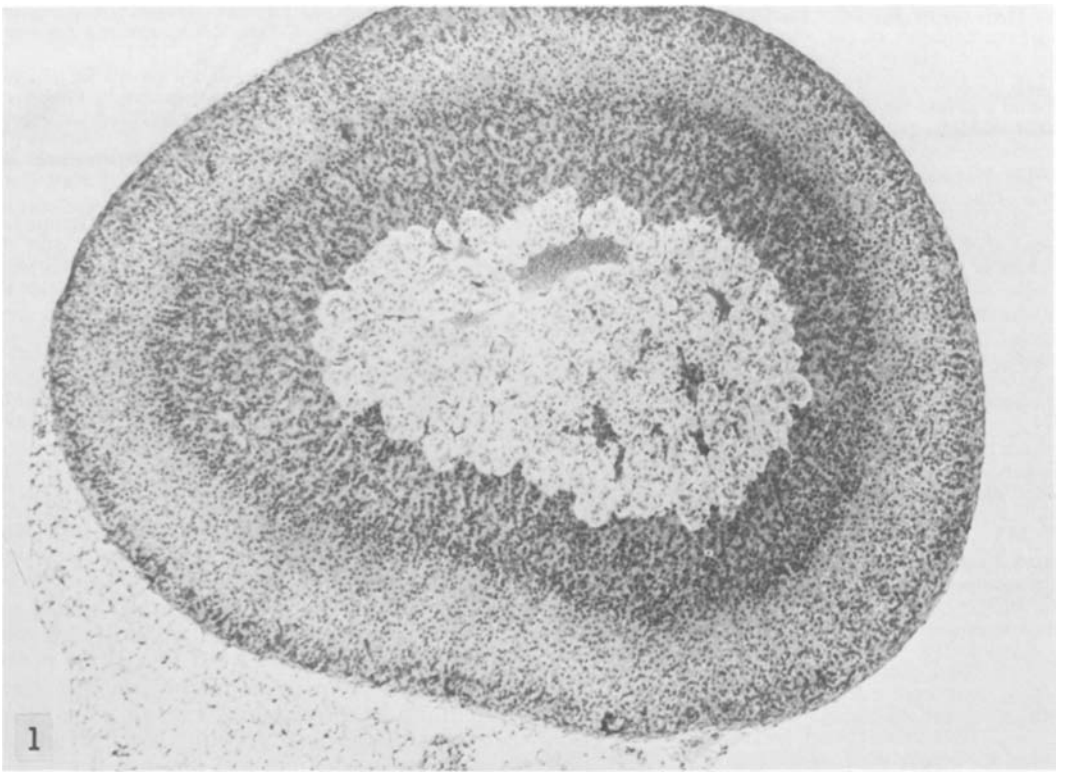
Figures 1–7.—Adrenal glands of virgin female mice. Hematoxylin-eosin-phosphomolybdic acid-light green.



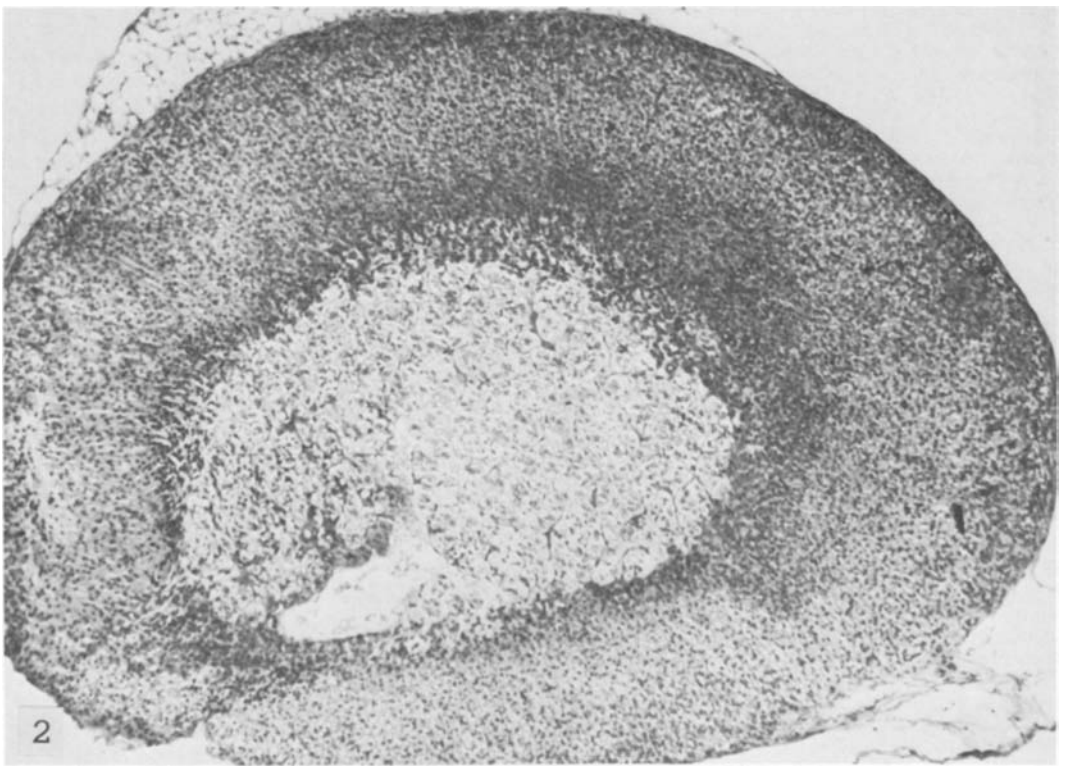



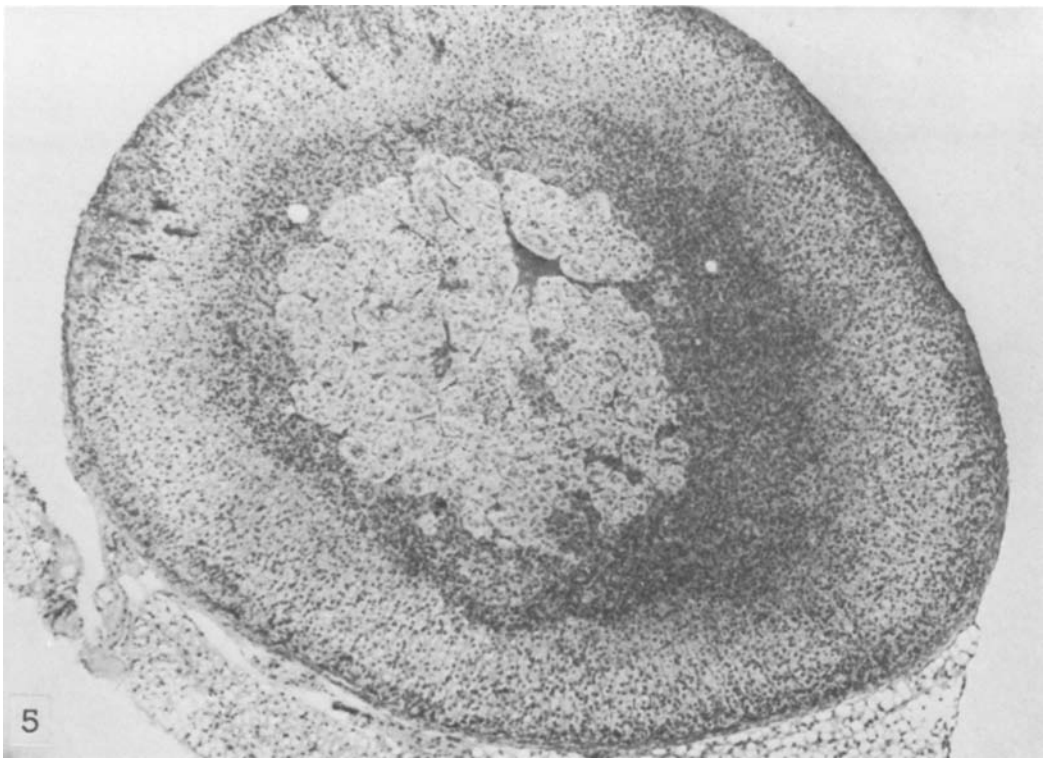

FIGURE 1.—SJL/J mouse 2 months old. *Note* broad zona reticularis and reduced width of zona fasciculata. ×36

FIGURE 2.—C57BL/6 mouse 2 months old. *Note* broad zona fasciculata and absence of zona reticularis. ×40



FIGURE 3.—SJL/J mouse 5 months old. *Note* persistence of zona reticularis. × 40

FIGURE 4.—C57BL/6 mouse 5 months old. *Note* absence of zona reticularis. × 36



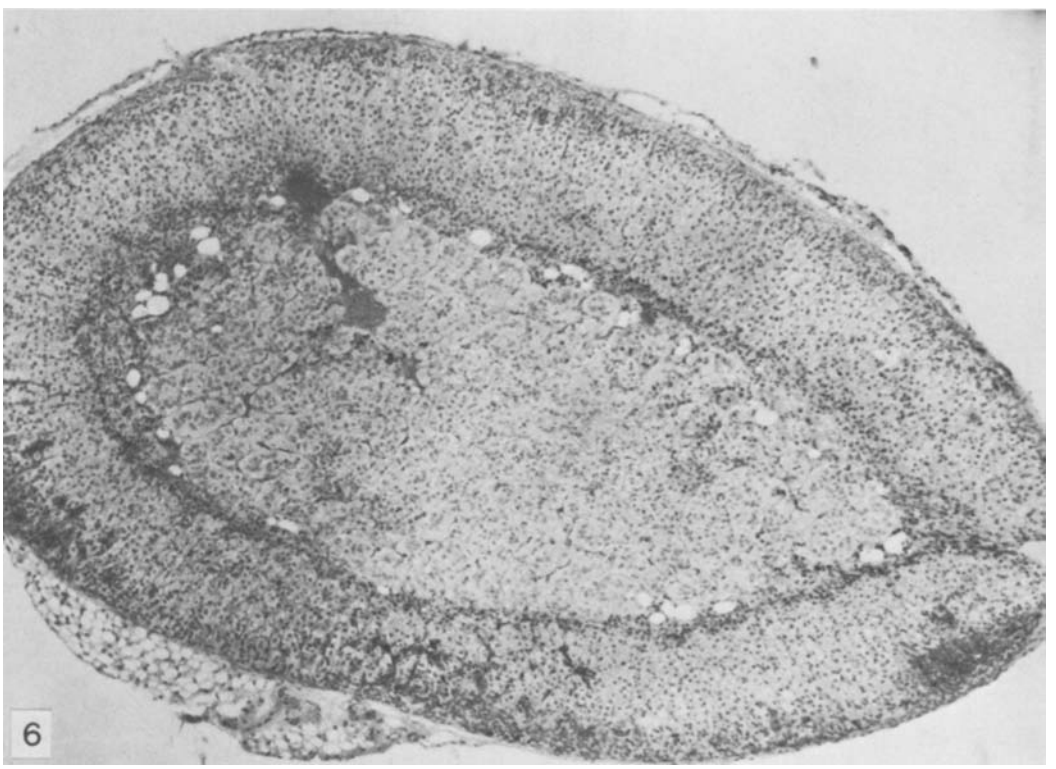




FIGURE 5.—SJL/J mouse 7 months old. *Note* persistence of zona reticularis. × 32

FIGURE 6.—SJL/J mouse 8 months old. *Note* remarkably reduced width of zona fasciculata. × 36

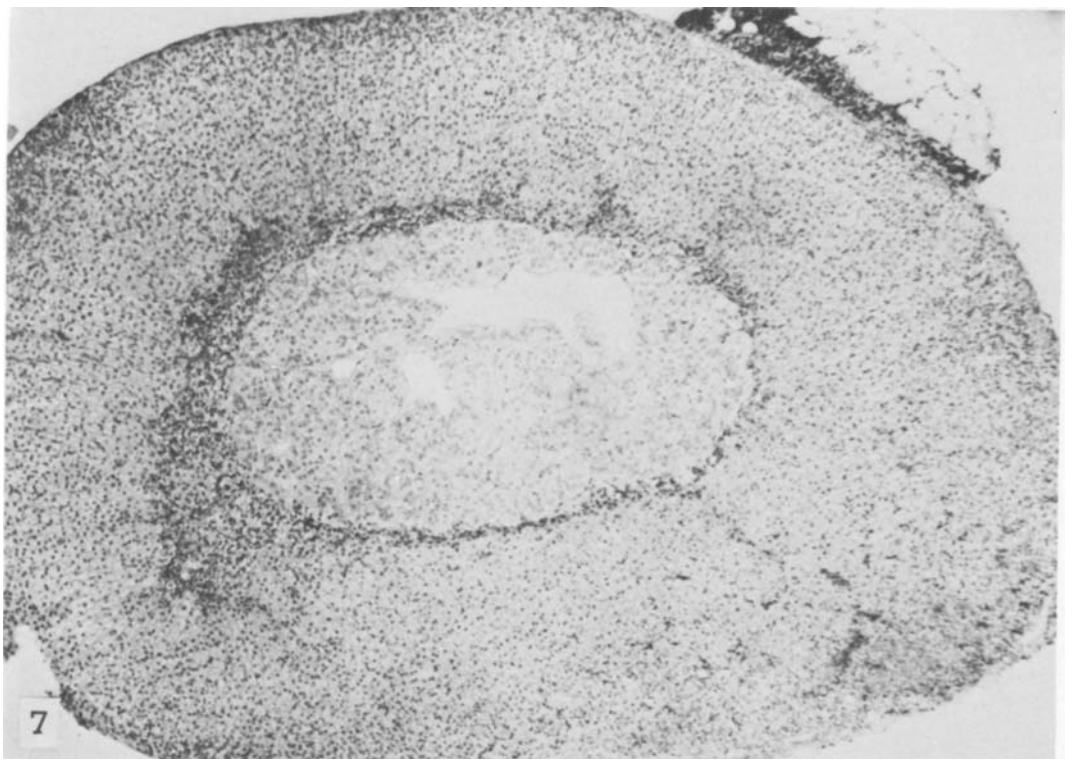



FIGURE 7.—C57BL/6 mouse 8 months old. *Note* normal width of zona fasciculata. ×40

**Figures 8–12.—Ovaries of virgin female mice. Hematoxylin-eosin-phosphomolybdic acid-light green.**

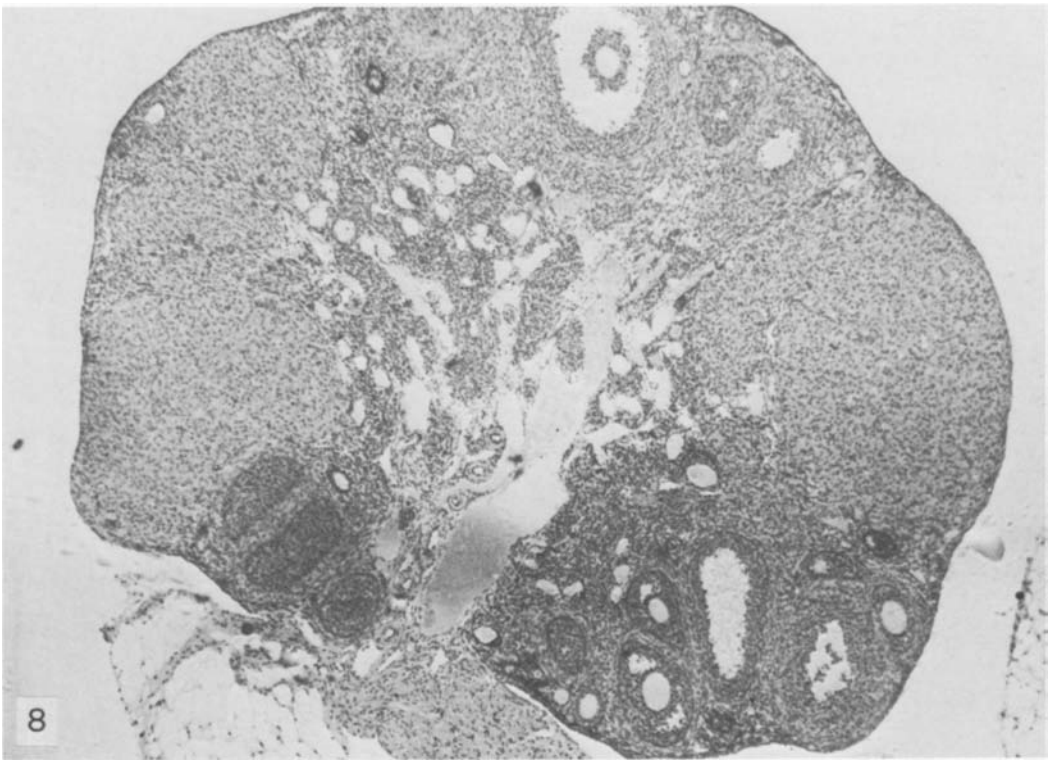
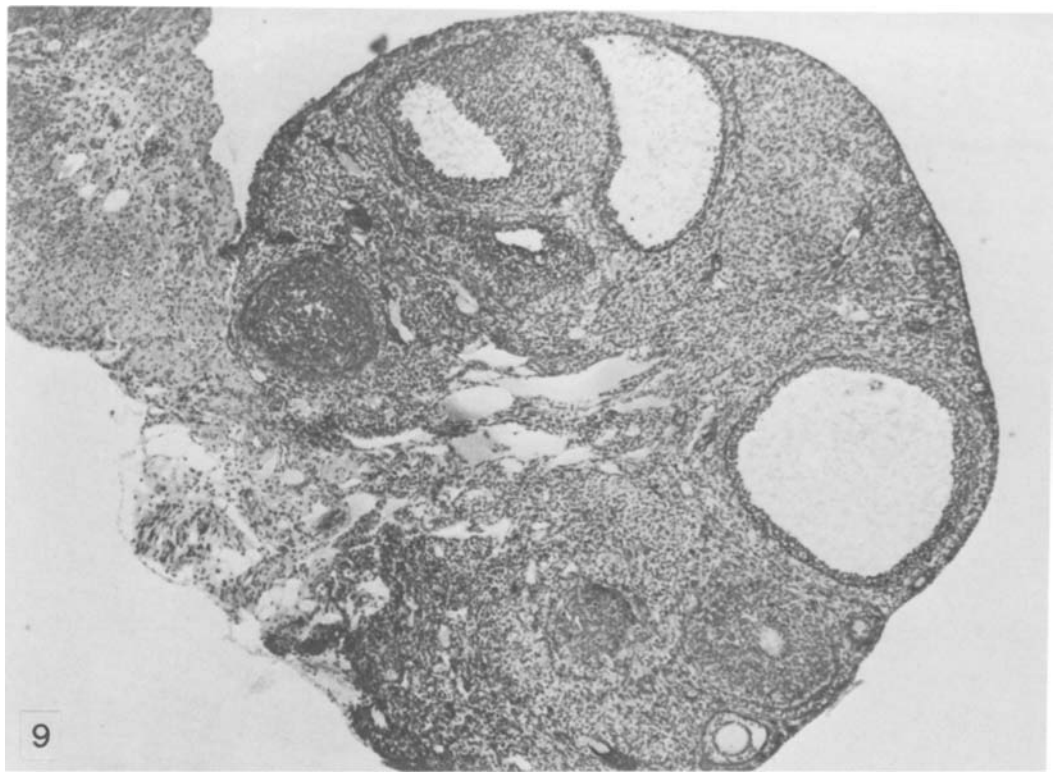



FIGURE 8.—SJL/J mouse 5 months old. *Note* large corpora lutea and follicles at different stages of maturation. × 28



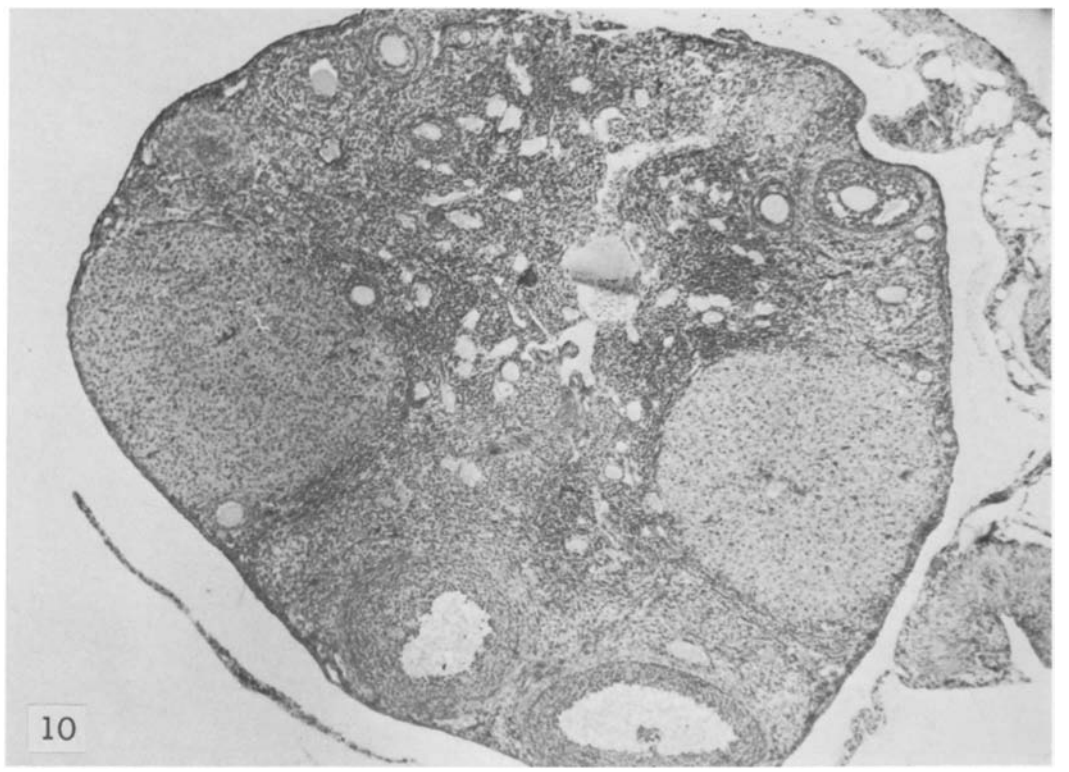




FIGURE 9.—C57BL/6 mouse 5 months old. × 32

FIGURE 10.—SJL/J mouse 8 months old. *Note* large corpora lutea and initial atrophy of residual part of gland. × 28

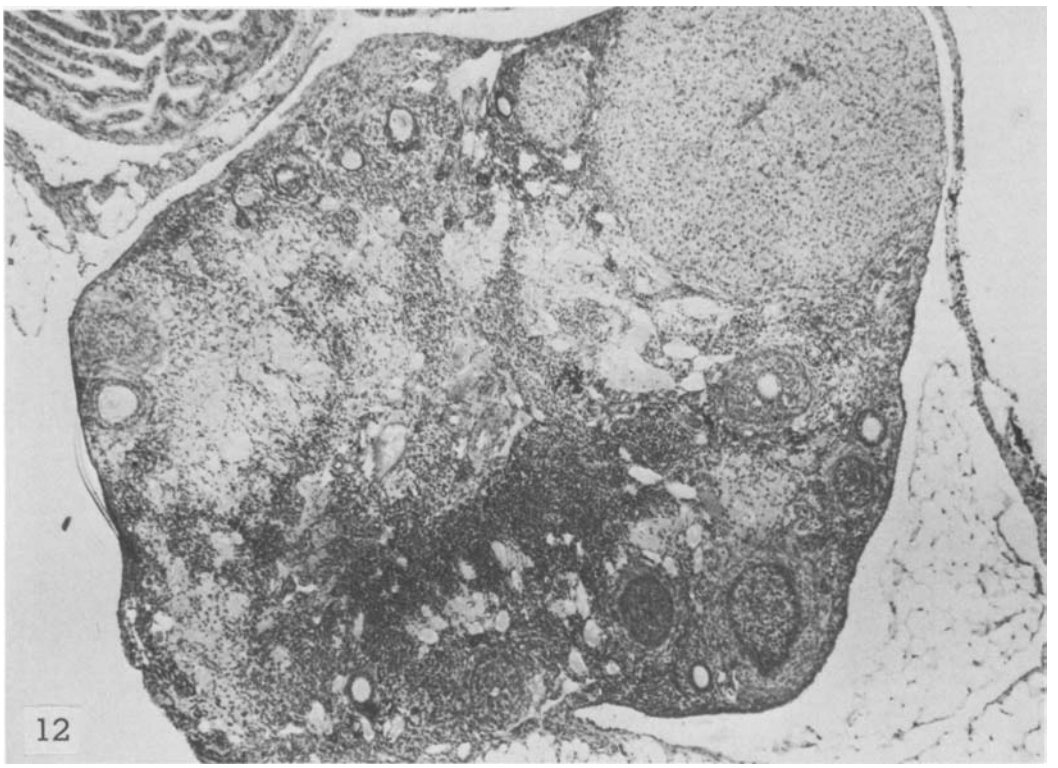




FIGURE 11.—SJL/J mouse 9 months old, bearing large reticulum cell neoplasm. *Note* large corpora lutea and initial atrophy of residual parts of gland. × 28

FIGURE 12.—SJL/J mouse 12 months old. *Note* persistence of large corpus luteum and advanced stage of sclerosis of residual parts of gland. × 32

Figures 13, 14.—Identically oriented and located sections of the anterior pituitary glands of 5-month-old virgin SJL/J and C57BL/6 females. Gluteraldehyde-osmium. × 10,000

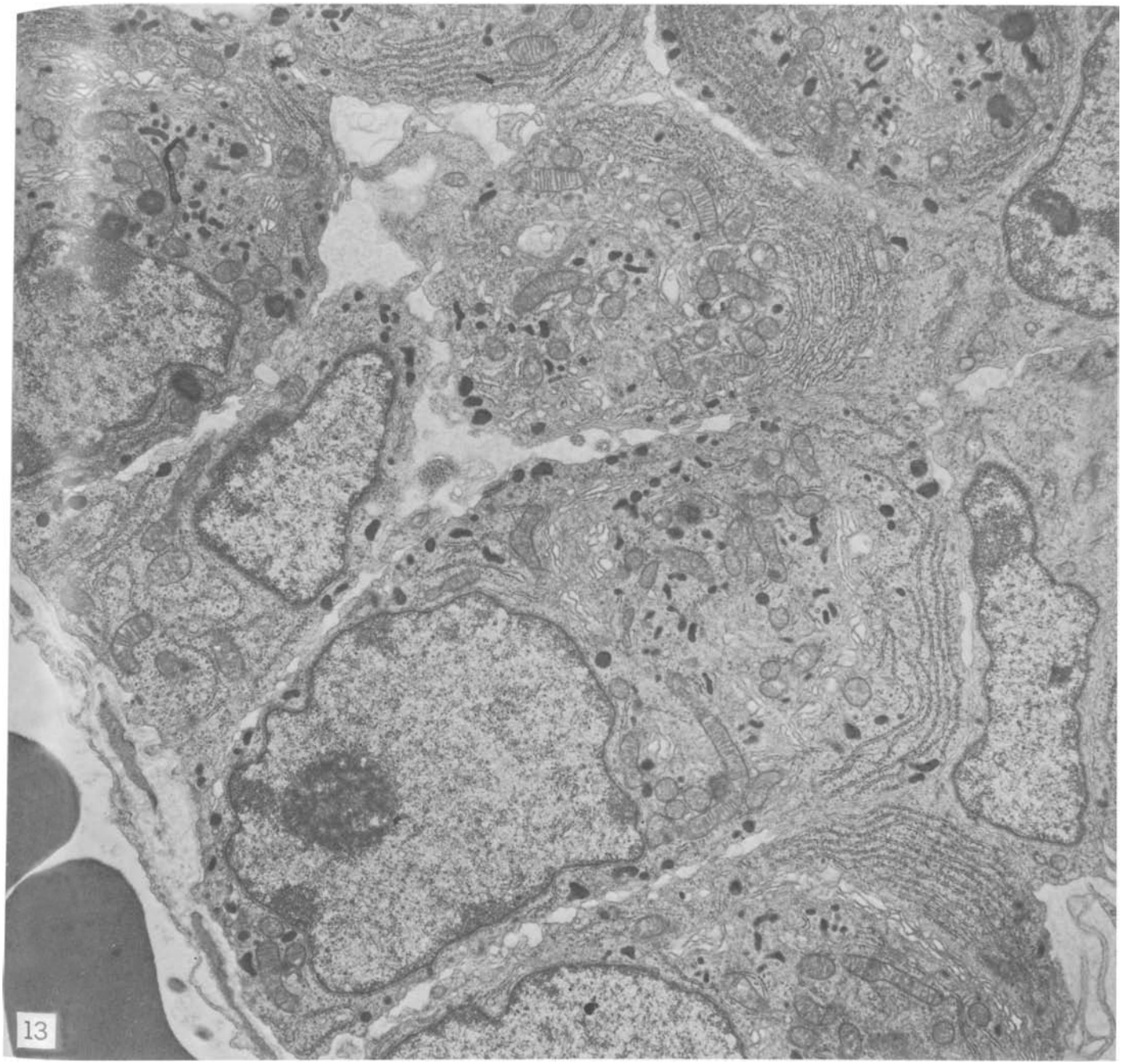



FIGURE 13.—SJL/J mouse. The field is completely occupied by gonadotropin-producing cells containing typical polymorphic hormone granuli (luteotropic hormone-producing cells).

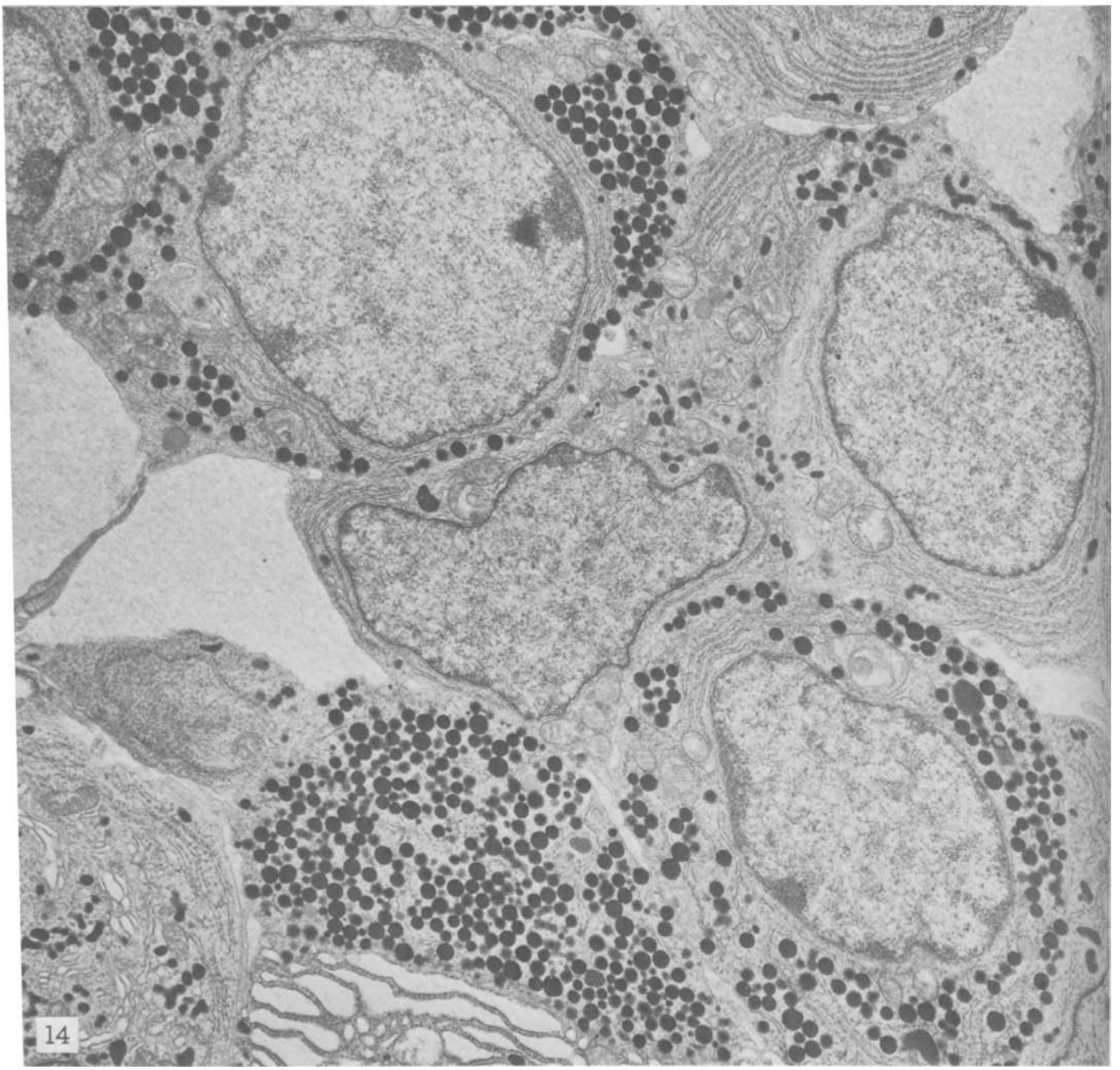



FIGURE 14.—C57BL/6 mouse. *Note* prevalence of growth hormone-secreting cells containing typical round hormone granuli in cytoplasm.